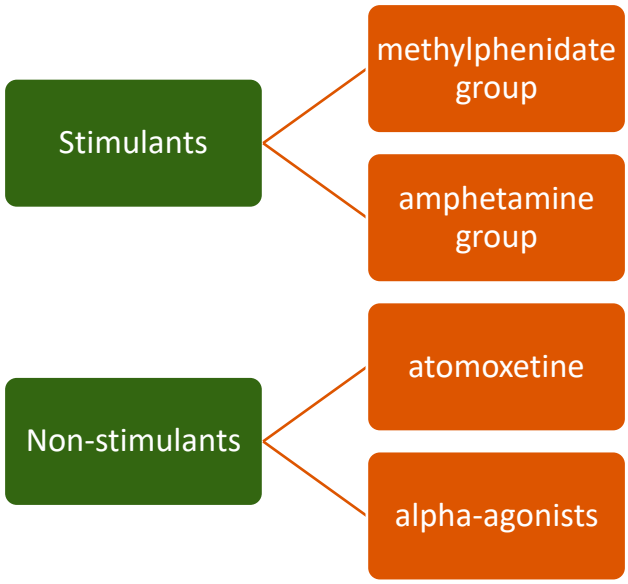
Mental health care in the pediatric clinic

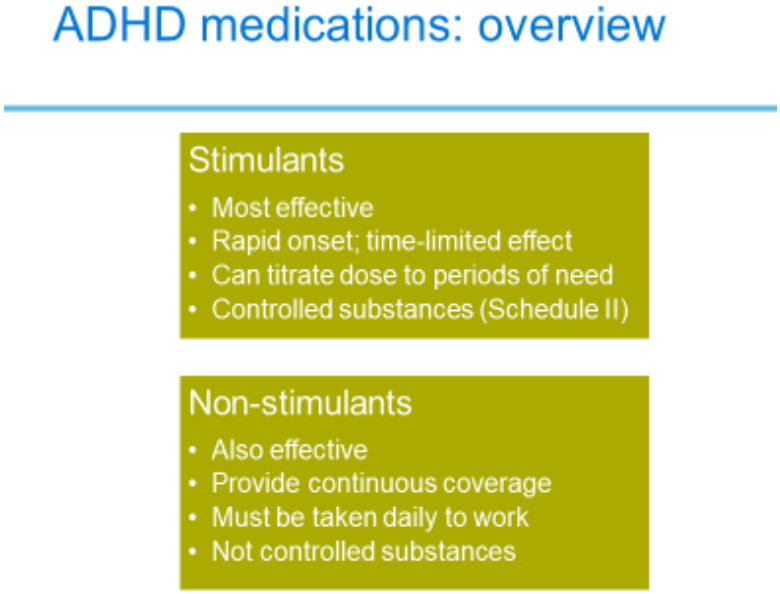
ADHD, Part 2

Objectives

Outline the range of stimulant medications, their benefits and side effects, and how to use them in treatment of ADHD.

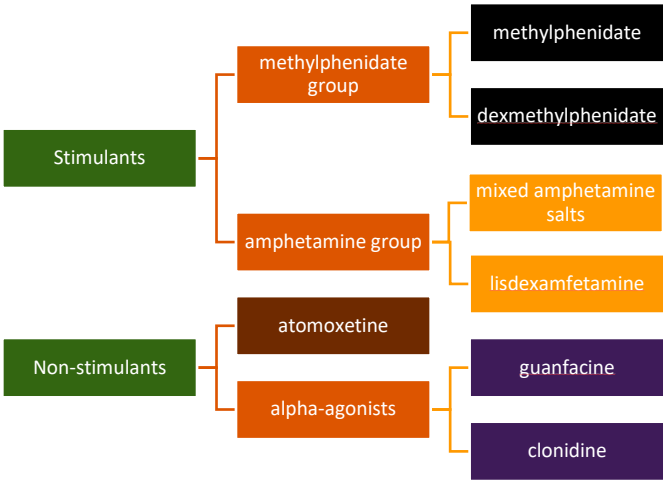
Now that we have walked through a case and some of the evidence base for treating ADHD, let's look at the whole landscape of ADHD medications. Pharmacotherapy for ADHD includes the stimulants and the non-stimulants. Stimulants are considered first-line treatment because of their effectiveness, versatility, and tolerability. Non-stimulants are also effective and provide continuous coverage when taken daily as prescribed. Non-stimulants are used alone or as augmentation to stimulant medications.





Stimulants fall into 2 groups: the methylphenidate group and the amphetamine group. Non-stimulants include 2 separate classes of medication: atomoxetine, and the alpha-agonists.

Here is the same taxonomy with individual medications included:



Stimulants- effects

- Up to 96% of patients improve on one of the stimulants
- Stimulant effects vary within domains (response isn't global)
    - Academic
    - Cognitive
    - Behavioral
    - Social

We will review the stimulants as a group and individually and address non-stimulants in next chapter. Stimulants are among the most effective medications in psychiatry. Up to 96% of patients will have ADHD symptom improvement on one of the stimulants. Response may vary across domains impacted by ADHD symptoms, and dose curves vary within and between individuals.

Listed here are some of the areas in which stimulants can improve functioning which is impaired by ADHD. Stimulants improve attention and decrease impulsivity. They tend to decrease impulsive aggression and oppositional behavior.
Socially, stimulants reduce the burden of hyperactive and impulsive behavior on others around the child, and also allow the child to better pay attention to social cues. As the child's behavior improves, parents and teachers tend to become more positive and less controlling, which creates a positive feedback loop.

Stimulant Effects: Cognitive

- Increase sustained attention
- Decrease distractibility
- Decrease impulsivity
- Improve short term memory
- Enhance use of learned strategies
- Improve motivation
- Improve frustration tolerance

Stimulant Effects: Interpersonal

- decrease off-task behavior
- increase compliance to instructions
- decrease intensity of behavior
- decrease oppositionality
- decrease aggression
- decrease impulsive conduct problems

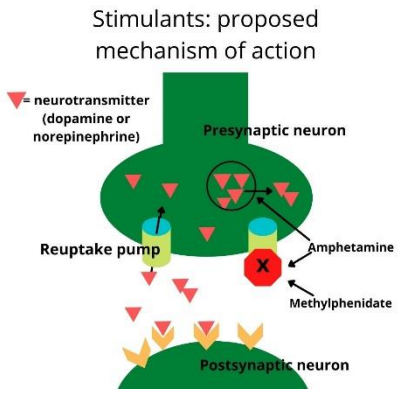
Stimulant Effects: Motor

- Decrease activity
- Decrease vocalization
- Less classroom noise and disruption
- Improve handwriting

Stimulant Effects: Academic

- Increase # completed and decrease errors in math problems at level child has learned but needs practice
- Increased productivity in
    - Reading comprehension
    - Sight vocabulary
    - Spelling
- Increased percentage of seat work completed

Stimulant mechanism of action:



Stimulants work by blocking the reuptake of both dopamine and norepinephrine on the presynaptic neuron, increasing the amount of neurotransmitter available in the presynaptic cleft. This is true of both major classes of stimulants, the methylphenidate class and the amphetamine class. The amphetamine class also enhances presynaptic dopamine release.

Now we will look specifically at the methylphenidate group. This chart shows the duration of action, starting dose and FDA-approved daily maximum doses of commonly used methylphenidate and dexmethylphenidate preparations.

The ADHD medication facts we are presenting here is as up to date as possible, but there are frequent changes in the field. Be sure to check your formularies.

Methylphenidate group

Generic/Brand Name(s)	Typical starting dose	FDA Max Dose/Day	Expected duration (hours)
immediate release methylphenidate and dexmethylphenidate formulations			
methylphenidate hcl tablet, chew-tab, oral solution Methylin®, Ritalin®	5 mg am & noon	60 mg	4
dexmethylphenidate tablet Focalin®	2.5 mg am & noon	20 mg	4
methylphenidate hcl and dexmethylphenidate extended release formulations			
Metadate ER® tablet	10 mg	60 mg	8
Metadate CD® capsule	20 mg	60 mg	8
Methylin ER® tablet	10 mg	60 mg	8
Ritalin LA® tablet	20 mg	60 mg	8
Ritalin SR® tablet	10 mg	60 mg	8
Concerta® OROS tablet	18 mg	72 mg	10 to 12
Aptensio XR® capsule	10 mg	60 mg	12
Daytrana® patch	10 mg	30 mg	10 to 12
Quillivant XR® suspension	20 mg	60 mg	10 to 12
QuilliChew ER® chewable	20 mg	60 mg	10 to 12
dexmethylphenidate extended release Focalin® XR capsule	5 mg	30 mg	8

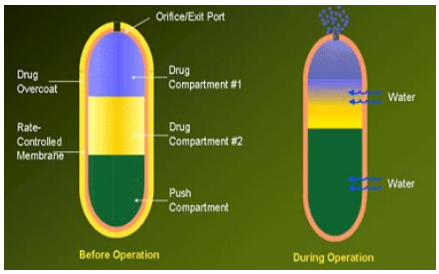
Immediate release (short acting) methylphenidate and dexmethylphenidate

- Last about 4 hours
- Generally dosed morning, noon, and 4 pm
- Tablet forms may be crushed and mixed with soft food
- Methylphenidate: 10, 20 mg tablets
- Dexmethylphenidate: 2.5, 5, 10 mg tablets
- Dexmethylphenidate dosing is ½ that of methylphenidate

Pharmacokinetics of extended-release stimulants

The extended-release stimulants are designed to mimic multiple doses of immediate release, or IR, formulations of the drug given every three hours. Some extended-release formulations mimic 2 doses, and last between 7 and 10 hours, and others, including methylphenidate ER and methylphenidate XR oral suspension, mimic 3 doses and last up to 12 hours.

Methylphenidate ER (Concerta®)



Non-soluble shell passes intact through GI tract
- Can't grind and snort drug
- Ineffective if cut or crushed
- Must be swallowed whole

Methylphenidate ER is designed to give 3 pulsed doses of methylphenidate, one immediately followed by 2 more each about 4 hours apart. The conversion from short-acting methylphenidate to methylphenidate ER is shown here. The dosing numbers appear off because 1 mg of methylphenidate is lost for every 5 mg of active medication.

5 mg MPH tid = 18 mg methylphenidate ER daily
10 mg MPH tid = 36 mg methylphenidate ER daily
15 mg MPH tid = 54 mg methylphenidate ER daily

Some patients (especially adolescents) may require and tolerate 72 mg (FDA approved max)

Methylphenidate extended-release transdermal patch (Daytrana®):

Another methylphenidate delivery method is the transdermal patch which is an effective option for children who cannot swallow pills or who have persistent GI discomfort with an oral stimulant. It also lasts for about 12 hours, although the patch is removed after 9 hours. The methylphenidate patch can cause skin irritation at the patch site. The manufacturers recommend switching the patch out from area of the hips and low back to another daily to reduce local irritation.

- Applied daily –
  - Worn for 9 hours for 12 hour duration
  - Effect within 1-2 hours
  - Lasts 3 hours after removed
  - Can remove sooner for shorter duration
- May see skin irritation at patch application site
- Remove for MRI – skin burns if metal in backing of patch
- FDA warning June 2015 of very rare side effect – permanent loss of skin color (chemical leukoderma)
- May cause a systemic allergy to MPH, prohibiting further use in any form.

Methylphenidate transdermal patch dosing:
Start with 10 mg patch and titrate up
Conversion from MPH sustained release formulation:

Total daily dose (mgs)

Sustained Release	Patch
10-20	10
25-30	15
35-40	20
45-55	30

Dexmethylphenidate immediate release and XR (Focalin®, Focalin XR®)

Dexmethylphenidate is the D-isomer of methylphenidate. It comes in an IR form that lasts about 4 hours, similar to methylphenidate, and an extended-release form that incorporates 2 pulsed doses and lasts about 8 hours. Children who need ADHD symptom control after school hours may benefit from a supplemental

dexmethylphenidate IR dose after school. This dose should be half of the XR dose. Because dexmethylphenidate is the d-isomer, dosing is half the methylphenidate dose.

- D-isomer of methylphenidate
- Theoretically less side effects
- XR form lasts 7-8 hours (equals 2 pulsed IR doses), so after school dosing of IR form is needed for many children
- XR capsule can be opened and mixed with small quantity of applesauce
- Dosing is ½ methylphenidate dosing:
  dexmethylphenidate XR 5mg = dexmethylphenidate IR 2.5 mg am and noon = methylphenidate CD 10 mg = MPH IR 5 mg am and noon = methylphenidate ER 18 mg = MPH IR 5 mg am, noon and 4 pm
  (methylphenidate ER contains the third dose, but strength is the same).

Amphetamine-related stimulants

The amphetamine-related stimulants are listed here. For the most part, they are all variations on amphetamines and mixed amphetamine salts, and differ in the form of administration and duration of action. The upper section of the chart shows the immediate release formulations, and the lower part the extended-release formulations.

Amphetamine-related group			
Generic/Brand Name(s)	Typical starting dose	FDA Max Dose/Day	Expected duration (hours)
Immediate release amphetamine formulations			
Adderall® (amphetamine mixed salts tablet)	5 mg am & noon	40 mg	4 to 5
Procentra Oral Solution® (d-amphetamine solution)	5 mg am & noon	40 mg	4 to 5
Evekeo® (d-and l-amphetamine tablet)	5 mg am & noon	40 mg	4 to 5
Zenzedi (d-amphetamine tablet)	5 mg am & noon	40 mg	4 to 5
Extended release amphetamine formulations			
Adderall XR® (amphetamine extended release mixed salts capsule)	5-10 mg	30 mg	8 to 10
Dexadrine Spansule® (d-amphetamine sulfate extended-release capsule)	10 mg	40 mg	8
Vyvanse® (lisdexamphetamine capsule)	20 mg	70 mg	10 to 12
Dyanavel XR® (amphetamine extended release oral suspension)	2.5-5 mg	20 mg	13
Adzenys XR-ODT® (amphetamine ext-release orally disintegrating tablet)	6.3 mg	18.8 mg	10

Mixed-Salts Amphetamine (MS-AMP, Adderall®, Adderall XR®, others)

- MS-AMP IR (immediate release) tablet (4-6 hour duration of action)
- MS-AMP XR (extended release) capsule (10-12 hour duration of action)
  - Equivalent to
    - methylphenidate TID
    - MS-AMP IR BID

The unit dose of immediate-release mixed-salts amphetamine lasts a little longer than does a dose of immediate-release methylphenidate. The extended-release form mimics giving 2 doses about 4-5 hours apart, and can come close in duration of action to methylphenidate given 3 doses. Some patients will still need a supplemental after school dose.

Lisdexamfetamine dimesylate (Vyvanse®)

- Amphetamine pro-drug
  - d-amphetamine bound to *l*-lysine
- Rapidly absorbed
- Rate-limited hydrolysis in liver and gut

- Once daily – effective from 1.5 hours after dose until 12 hours after dose
- Lower abuse potential, but still Schedule II

Dosing

- Start with 20-30 mg and titrate up by 10 mg increments
- Maximum recommended dose 70 mg
- Capsule may be opened and sprinkled on food or dissolved in water

Prohibitive Stimulant Side Effects: Reduce dose or change medication

Stimulant side effects involve primarily the gastrointestinal and neurological systems. They can include anorexia and abdominal pain, insomnia, headaches, and mood and behavioral changes. Stereotypies such as picking at skin, pulling hair or eyebrows, or biting lips may occur. Some children become more emotional, others feel that their personality is dull and that they cannot have fun. Hallucinations are quite rare and generally appear as visual hallucinations of bugs or animals, or tactile hallucinations. These side effects are all reversible with reduction or cessation of the medication.

- Severe anorexia
- Severe insomnia (> 1.5 hr)
- New, marked, severe tics or picking behavior
- Severe, unrelenting headaches
- Intolerable abdominal pain
- Severe irritability, leading to aggression
- Severe depression, not pre-existing
- Hallucinations
- Dulling of personality "zombie"-like

Major Stimulant Side Effects: Reduce dose or change medication

The same side effects can present in more moderate forms, and again, you will generally want to consider a dose reduction or alternate medication, especially if the symptoms persist more than a week or so.

- Moderate anorexia
- Moderate insomnia (1-1.5 hr)
- Moderate headaches
- Moderate abdominal pain
- Moderate increase in picking skin, nail biting
- Moderate irritability
- Moderate depression not pre-existing
- Mild constriction of personality

Minor Stimulant Side Effects: expected, may be tolerable

When these side effects are mild, decisions about management come down to a balancing any benefit gained from the medication with the burden of side effects. This balancing should include the viewpoint of the child as well as parents and yourself. If a child really does not like the way he feels when taking a stimulant medication, you should consider trying a different medication.

- Mild anorexia
- Mild insomnia (< 1 hr)
- Mild headaches
- Mild abdominal pain
- Mildly increased irritability
- Mildly increased picking at skin, nail biting

Dealing With Stimulant Side Effects
For appetite loss

- give stimulants with meals
- add a high-calorie drink or snack in the evening when stimulant effects have worn off
- Consider use of cyproheptadine (4 mg nightly, or bid if not sedating) to stimulate appetite.

Appetite loss is generally worst at midday when the stimulant is effective. Increasing caloric intake at breakfast and later in the day can keep weight steady. If a child has good ADHD symptom control with a stimulant but weight gain is poor, consider prescribing the antihistamine cyproheptadine, which has the side effect of increasing appetite. While there is not extensive literature supporting its use in stimulant-induced weight loss, it has been found effective for treating poor appetite and weight loss in pediatric patients with cystic fibrosis and functional gastrointestinal disorders.

Stimulants and Sleep
Assess baseline pre-medication sleep patterns
Sleep problems are common in children with ADHD and are also common with stimulant treatment.
Consider other causes of sleep problems and review sleep hygiene

- ADHD symptoms
- Oppositional behaviors at bedtime
- Poor sleep habits - overstimulation
- Separation anxiety

Stimulant effect: are the stimulants affecting sleep? If so, consider shorter acting formulation or earlier dosing
Stimulant rebound: too hyped to sleep due to rebound? Consider melatonin, consider clonidine 0.05-0.1 mg at bedtime

Dealing With Stimulant Side Effects: emotional changes
Some children experience emotional side effects to stimulants:

- Sadness
- Irritability
- Constriction or dulling of personality

If these occur, reduce dose or change medication.
Some will do well during the day but have rebound irritability when the stimulant wears off. For these children, consider additional low-dose immediate release stimulant later in day; monitor effect on sleep.

Cardiac screening
Take cardiac history of patient and family: further assessment is needed if there is:
Family history

- Early or sudden cardiac death
- Arrhythmias

Patient history

- Structural abnormalities
- Chest pain
- Palpitations
- Fainting episodes

AAP guidelines on cardiac monitoring

At one point, it was thought that all patients should have a screening ECG prior to stimulant use. This was because of a potential correlation between stimulants and serious cardiac events in some very large population studies. The questions about universal screening with ECG for stimulant use are similar to those in questions about universal ECG for athletic participation. Eventually the AAP and American Heart Association settled on the recommendations outlined in this 2008 algorithm. As you can see, ECG, and possibly cardiology consultation, are only indicated if there are indications of possible heart disease in the history and/or physical exam.

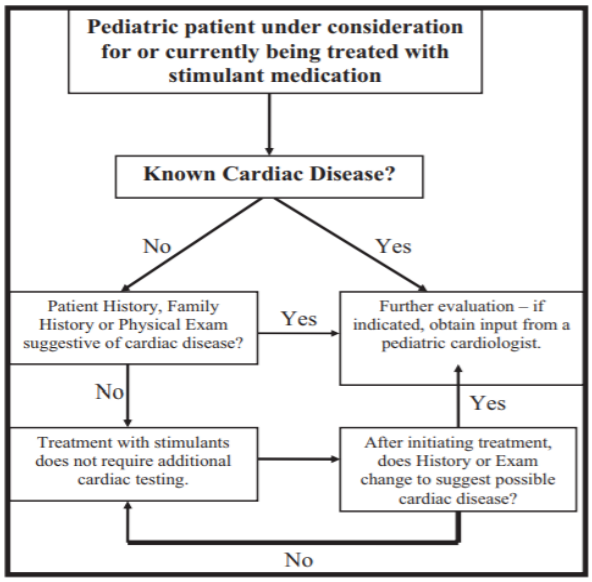


FIGURE 1
Cardiac evaluation o
lant medications.

Perrin et al, PEDIATRICS, Volume 172, Number 2, August 2008

Seizures: No research evidence to support stimulant-caused increased risk of seizures in patients with ADHD

Tics or Tourette's syndrome and stimulants

Consider the natural history of tics and Tourette's syndrome: they tend to wax and wane in severity over time

Most tics do not worsen with stimulant treatment of ADHD

Consider cost/benefit ratio: do benefits of lowering ADHD symptoms outweigh costs of some tics?

Are ADHD symptoms more impairing than tics?

Consider augmentation with alpha-agonist which may reduce tics

Linear Growth and stimulants

- Studies are inconsistent re impact of stimulants on final height but a recent analysis of data from participants in the MTA Study suggests that there may be as much as 1.6 inches in reduced growth among patients who consistently used stimulants for 16 years. (Greenhill et al, J Am Acad Child Adolesc Psychiatry. 2020 Aug;59(8):978-989)
- Monitor height and weight
- Adjust foods and mealtimes
- Catch-up growth may occur when off medication

Drug Abuse and stimulants

- No evidence for stimulant-induced increase
- Effective ADHD treatment may decrease drug abuse
- Drug abuse more likely with comorbid ODD or Conduct Disorder
- Monitor medication carefully- diversion is a high risk
- If misuse is a risk, consider
  - methylphenidate ER
  - methylphenidate transdermal patch
  - lisdexamfetamine
  - Non-stimulant

Adela

Adela is a shy, quiet child whom you have seen since birth. She is now 9, in 4th grade. Third grade was a little rocky- as reading assignments lengthened and they started word problems, Adela would drift off or give up part way through.
Adela is cautious, not a risk taker, a bit of a worrier, but she and her mother deny sustained worry or anxiety interfering with activities, sleep, or appetite. Adela's mother's brothers both have ADHD.

You give Vanderbilt scales which mother brings back at the return visit.
Parent: inattention: 22 hyperactivity: 6
Teacher: inattention: 25 hyperactivity: 7
You have ruled out other causes for inattention; no medical problems, normal vision and hearing, no trauma history.
Adela is mildly anxious around other people, but even at home when she is relaxed, she is inattentive.

You discuss stimulant medications with Adela and her mom.
They have many questions.

Do I have to take it every day?

- I recommend that you take it every day, especially as you are getting started with it. Being able to focus on the weekends is important, and you will probably find that you feel more productive.

This is a common first question. I generally recommend that patients take their stimulant medication every day, especially at the beginning. Recall that the MTA study found that children had better results when they took their medication 7 days a week. Pharmacologically, however, it is not essential to take a stimulant daily. Each dose is as effective as any other dose.

Is it addictive?

- When you take this medication for your ADHD, you will not get addicted to it, and you won't have withdrawal symptoms if you don't take it.
- It is a controlled substance, though, which means that some people use it who don't need it, and get addicted.

There is no evidence for physiologic or psychological dependence to stimulant medication in patients with ADHD using medication as directed.

Will it change my personality?

- It shouldn't. It should improve your focus, and sometimes when people are paying attention better it changes how they interact with others, and that can be a good thing. But if there is anything you don't like about the way you feel with the medication, let me know, and we will talk about it.

Some patients find that they get along better with others when they can slow down, pay attention better, and have better impulse control. Sometimes, though a type or dose of medication can make kids feel as though their personality is constricted, and they can't have fun, or they don't make people laugh like they used to. These concerns should be taken seriously, and the medication adjusted or changed.

How long will I have to take it?

- For as long as it is helpful, and you want to take it. Medication does not cure ADHD; it treats the symptoms when you take it.

- As you get older, you may find that you develop organizational skills that make up for your difficulty with attention, or that your inattention gets better.
- However, 30 to 80% of children with ADHD continue to have symptoms into adolescence and up to 65% into adulthood.

Medication does not cure ADHD, it treats symptoms when present. Some patients will "outgrow" ADHD symptoms as they get older or develop compensatory skills sufficient to functioning despite their inattention.

Adela

You start Adela on methylphenidate ER 18 mg, with modest response. You increase to methylphenidate 27 mg.
Vanderbilt rating scales:
Parent: inattention: 5 hyperactivity: 6
Teacher: inattention: 6 hyperactivity: 3

Adela is pleased with her improved ability to focus and get her work done.
She still has difficulty getting her homework folder from school to home and back every day.
During tests she gets distracted and a little anxious when other students start finishing up ahead of her.
She reports decreased appetite, and some difficulty getting to sleep.

Recall these components of ADHD treatment. Adela has good control of the core ADHD symptoms on methylphenidate ER, but she is still struggling with organizational skills and test-taking. Some of this may be related to her timidity- she may be nervous about asking for clarification of assignments, and embarrassed or worried when other children finish testing before she does. She may benefit from some specific supports at home and school. She should have a quiet place without distractions where she can do her homework daily. Her parents might help her check that her homework is put into her backpack every night before bed. At school, similar help can be requested through a 504 plan.

Academic support- 504 plan

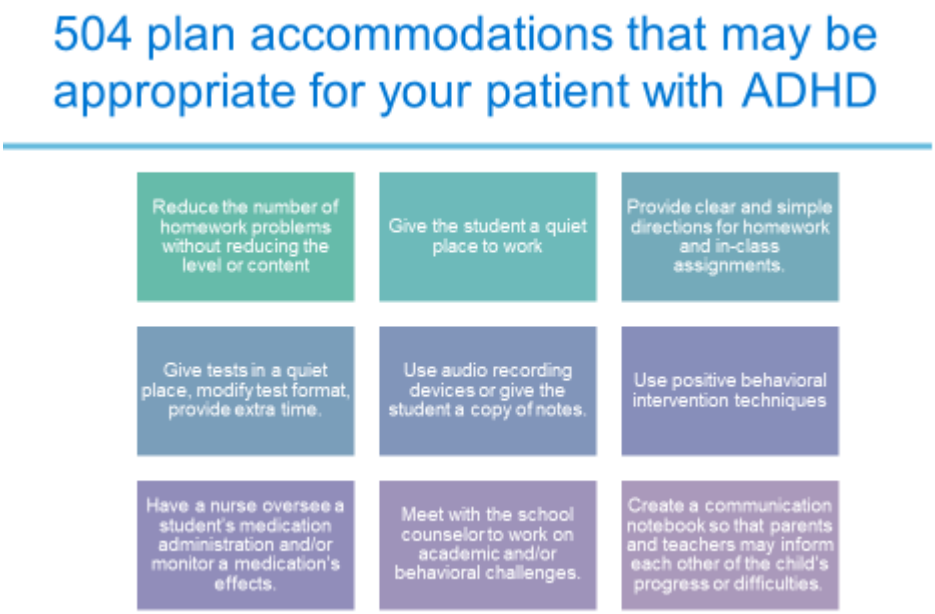
Most children and adolescents with ADHD can benefit from accommodations at school that mitigate the impact of ADHD symptoms on education.
Section 504 of the federal Rehabilitation Act of 1973 requires the needs of students with disabilities to be met as adequately as are the needs of the non-disabled.
Section 504 is not special education, and not the same as an IEP. Students with a 504 plan get standard education with accommodations to make that education possible.

Your role in helping your patient get a 504 plan.

Provide your patient with a letter stating

- Diagnosis
- Treatment

- How the diagnosis affects the child in the school setting (eg, why the diagnosis represents a disability)
- General recommendations for accommodations (you don't have to know exactly which accommodations are most appropriate)



Listed here are some of the accommodations that can be included in a 504 plan. These may vary over time. Younger children may need more help with organizing their notebooks, and older children may benefit from extended time for testing. Many children are given the option to take tests in a quiet room with fewer students to minimize distraction. You do not have to determine exactly what accommodations the child will get; that will be determined at a meeting at school.

Sample 504 plan letter template

To School Staff:
I am the treating physician for ***. *** is diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), combined type. *** is taking *** to help control symptoms. The ADHD affects *** in school in that *** has limited ability to focus on details, is easily distracted, has difficulty with organization, may not follow through on instructions, finds it hard to stay still, and may find it hard to wait their turn. Please provide *** accommodations under a 504 plan as appropriate to help with *** attention and hyperactivity issues. These can include preferential seating, making eye contact and ensuring that *** is paying attention to instructions, making sure *** understands when and where to turn in assignments, check in/check out procedures for organization, movement breaks, and extended time for testing.
Please contact me if you have questions or concerns.
Sincerely, Edison Sparks, MD

Summary

- ADHD is common and treatable.
- Medication treatment is effective for the core symptoms of ADHD.
- Parent management training, school accommodations, and remediation of academic or socials skills deficits may address behavioral and learning problems that accompany ADHD.
- Stimulants are first-line treatment for ADHD for most people.